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Introduction

Neurofibromatosis 2 (NF2) is an autosomal dominant disorder characterized by the development of multiple nervous system tumors. All subjects develop bilateral vestibular schwanomas that lead to deafness and death if untreated. Subjects also tend to develop multiple meningiomas and spinal tumors, which result in significant motor and sensory deficits if left untreated. In the past decade, great strides have been made in terms of radiographic diagnosis, surgical approaches to these tumors, and understanding of the molecular biology of NF2. Unfortunately, similar advances in the understanding of the natural history of these tumors, fundamental to the evaluation of treatments, have not yet been made. The purpose of this study was to define the growth rates and clinical course of tumors associated with NF2. We accomplished this goal through the following steps:

1. Developed an international consortium of clinical centers with expertise in NF2, further expanding the infrastructure developed in the Natural History of Vestibular Schwannomas in NF2 US Army grant. All subjects were evaluated at local centers with full neurological, ophthalmological, radiographical, and audiometric evaluations and the data were sent to a centralized center for analysis.
2. Developed standardized volumetric analysis of intracranial and spinal tumors.
3. Formed an infrastructure for use in future clinical trials. All NF2 subjects identified at clinical centers will be categorized as potential subjects for future clinical trials.
4. Examined molecular and clinical features which may predict tumor behavior.

This study led to a better understanding of the natural history and clinical course of tumors associated with NF2. An understanding of the natural history is also fundamental to the determination of efficacy of future medical or surgical therapies. Finally, the framework of clinical centers, data management, and scientific expertise established during this project could, if given further support, form the core for future treatment trials in NF2.

Body

STATEMENT OF WORK
NF2 Natural History Consortium

Task 1. Standardize Clinical Data Collection for NF2 Subjects

a. **Finalize proposed case record forms. (month 1): Completed**
All case record forms were created, finalized, and sent to all participating investigational sites. A Manual of Procedures, with the case record forms, has been sent to all investigational sites. The Manual of Procedures details the exact protocol to be followed to obtain the specified measurements in tumor size, hearing, eye evaluation, and quality of life and physical functioning.

b. Creation of Comprehensive Care database and tracking system (months 1-3): Completed
A coordinated system for collecting and transmitting study data was established.

As detailed in the Manual of Procedures, House Ear Institute (HEI) serves as the Statistical Analysis and Data Management/Coordinating Center for the project. Clinical Coordinators send all original data to HEI. A Central Tracking System was established at HEI to track each subject and assure the consistent inflow of data from each site.

Files for each subject have been created and kept in a locked cabinet. A computerized database has been created to house the study data. As forms are sent to HEI, the data are entered into the database.

c. Assist in translation of quality of life questionnaire and Comprehensive Care case record forms into Japanese and German (1-4): Completed
At the outset of the study, Japan was included as one of the investigational sites of the NF2 Natural History Consortium. However, since that time, Japan has withdrawn from participation and a new investigational site has been added in France. Questionnaires and case record forms were sent to both the France and Germany investigational sites.

d. Modify previous NF2 Natural History Consortium methods for data transfer to comply with extra requirements required for Comprehensive Care database (months 1-3): Completed.
Study methods have been created to ensure transmittal of data to HEI. Clinical Coordinators from each study site are in charge of contacting subjects, setting up appointments or receiving scheduling information from subjects, assisting with insurance authorizations, communicating facility name and contact information to the Project Manager at HEI and to WorldCare. The Clinical Coordinator also attends the subject's exams, ensures completeness of the exams, and fills out the MRI Examination Outcome form and Data Transmission CRFs.

The MRI Facility performs the cranial and spinal MRI exams according to protocol, fills out the MRI Data Acquisition CRFs and gives them to the Clinical Coordinator, and invoices the investigational site for the stipend for completing the CRF.

WorldCare received notification of subject information, exam date, and facility from the Clinical Coordinator. WorldCare ensures that test data are sent from the MRI facility to WorldCare and are acceptable.

Original, completed CRFs are sent to HEI. Queries regarding incomplete or inconsistent information on CRFs are answered by the Clinical Coordinator and WorldCare.

HEI tracks and monitors data flow, logs, dates and notes facilities, notes if data are received by WorldCare, follows up with the status of data.

Task 2. Standardize Volumetric Analysis of Intracranial Tumors and Spinal Tumors.

a. Development of standard operating procedure for digital analysis of MRIs (months 1-3): Completed

A Manual of Procedures is complete for the Investigators, Clinical Coordinators and WorldCare. The manual contains information for the data flow, acquisition protocol, and data transfer of images. WorldCare guidelines were merged with the HEI Manual of Procedures and were distributed to the Clinical Coordinators and Investigators at each investigational site.

b. Preparation of facilities at WorldCare, Inc. (month 1): Completed

A private suite for the NF2 Natural History Consortium has been prepared at WorldCare, Inc. At this time, all equipment and methods of sending and receiving data have been used for the collection and analysis of subject data. Also, the filing system, logbooks, and subject database are established to accept and track the workflow of subject data. An additional worksite has been set up next to the initial worksite to facilitate the radiologist reading the scans. The additional worksite has resulted in saving considerable time when transferring between images.

c. Perform test retest data of other cranial tumors and spinal tumors to determine amount of change required to be considered a statistically significant difference (months 1-3): Completed

Test/retest data has been collected for other cranial tumors, specifically meningiomas. Acquisition of test/retest data is complete. Analysis indicated that the test-retest reliability of other cranial tumors was similar to that of the vestibular schwannomas.

d. Perform qualitative and quantitative analysis of MRIs (months 4-33): Completed

Dr. Michael Lev, the Neuro radiologist in charge of reading the MRIs, indicated whether the MRI scans and corresponding data are acceptable to include in data analysis. Case record forms were checked to ensure accuracy of the data. Data cleaning was an ongoing process as data were received at HEI, entailing the checking of irregular data values, data editing, corrections and updating.

e. Collection of yearly MRI data (months 1-35): Completed

Of the subjects who have completed and have had the scans sent to WorldCare for analyzing for Year 1 84 (98%) cranial exams and 78 (91%) spinal exams have been received. Of the subjects who have completed the Year 2 exams, 74 (95%) cranial exams and 62 (79%) spinal exams have been sent. Of the subjects who have completed the Year 3 exams, 48 (91%) cranial exams and 40 (75%) spinal exams have been sent. Of the subjects who have completed the Year 4 exams, 23 (92%) cranial exams and 19 (76%) spinal exams have been sent. WorldCare has analyzed, and sent HEI 83 (99%) Year 1 Cranial MRI CRFs, 63 (85%) of the Year 2 Cranial MRI CRFs, 45 (94%) of the Year 3 Cranial MRI CRFs, 21 (91%) of the Year 4 Cranial MRI CRFs. WorldCare has analyzed, and sent HEI 76 (97%) of the Year 1 Spinal MRI CRFs, 46 (74%) of the Year 2 Spinal MRI CRFs and 33 (83%) of the Year 3 Spinal MRI CRFs, 14 (75%) of the Year 4 Spinal MRI CRFs.

Task 3. Prepare International Consortium of Clinical NF2 Centers.

a. Modify previous NF2 natural history database for additional requirements of this study: Completed

The NF2 Natural History Database has been modified to include data for visual tests, quality of life and physical functioning questionnaires as well as modifications to CRFs for subject medical history, MRI, audiology, neurological, and molecular biology exams.

b. Obtain local IRB approval (months 1-2): Completed

Eight of the nine study sites have received local IRB approval. New York University did not receive local IRB approval and was withdrawn from the study.

c. Obtain Army IRB approval and single project assurance approval (months 2-18) Completed

Of the nine sites that are participating in the study, all but one domestic site and one foreign site have received Army IRB approval and project assurance

SITE	APPROVAL
House Ear Institute	11/01/01
University of Texas	03/25/02
Massachusetts General Hospital	09/23/02
Royal Victorian Eye and Ear Hospital	10/10/02
Ohio State University	10/20/02
Universitatsklinikum Hamburg-Eppendorf	11/03/02
Hopital Beaujon	06/21/04

The two sites that did not receive approval are St. Mary's Hospital in England and New York University in New York.

d. Train centers on study protocol (spine, ophthalmology, quality of life, comprehensive care) (months 3-6): Completed

A meeting was held for all Clinical Coordinators and Co-Principal Investigators to review the study protocol. Study protocol and Manual of Procedures were distributed to each Co-Principal Investigator and Clinical Coordinator at each site. HEI maintains ongoing telephone discussions with the Clinical Coordinators to facilitate the study and the timely collection of data.

e. Train centers in data transfer to Data Management Center (months 3-6): Completed

All Clinical Centers have been given a Manual of Procedures informing them of the protocol for data transfer to the Data Management Center at HEI. Clinical Coordinators are responsible for sending all original, completed CRFs for audiology, neurological, and ophthalmology exams and medical history, SF-36 quality of life and physical functioning interview to the Project Manager at HEI. Original, completed MRI CRFs are sent to HEI by WorldCare.

Task 4. Subject Recruitment and Data Collection (month 3-30)

a. Enroll previous Natural History of Vestibular Schwannoma in NF2 subjects in current study: Completed

Some subjects elected not to enroll in the new study and some subjects were dropped by the local centers as they were non-compliant with the first study. The following subjects have been enrolled

Subject Collection Center	Location	Subjects Enrolled From Previous Study	New Subjects Enrolled	Total Subjects Enrolled
House Ear Institute	Los Angeles, CA	21	27	48
Massachusetts General Hospital	Boston, MA	9	4	13
St. Mary's Hospital	Manchester, UK	NA	NA	NA
Universitatsklinikum Hamburg-Eppendorf	Hamburg, Germany	11	0	11
New York University	New York, NY	NA	NA	NA
Royal Victorian Eye and Ear Hospital	Melbourne, Australia	4	1	5
Ohio State University Hospital	Columbus, OH	1	0	1
Hopital Beaujon	Paris, France	0	16	16
University of Texas, Houston	Houston, TX	0	2	2
Total Subjects Enrolled		46	50	96

NA – Sites that have not yet received IRB approval.

b. Individual centers identify potential subjects to replace subjects who dropped out: Completed.

Clinical Coordinators at each investigational site screened their subject population and identified potential subjects for the NF2 Natural History Consortium study. Enrollment closed December 31, 2005.

c. New subjects will complete baseline audiometric, MRI, neurological, ophthalmologic exams, SF-36 and physical functioning questionnaires and provide blood and tumor samples: Completed

Clinical Coordinators are responsible for ensuring subjects yearly exams. Although a subject may have completed an exam, it is not considered complete until the original copy is received at HEI and entered into the database. Of the 86 subjects who have completed the Year 1 exams, 77 (90%) audiology exams, 83 (97%) neurology exam, 84 (98%) ophthalmology exams, 81 (94%) SF-36 questionnaire and 82 (95%) Physical Functioning Interview. Of the 78 subjects who have completed the Year 2 exams, 70 (90%) audiology exams, 73 (94%) neurology exam, 61 (78%) ophthalmology exams, 77 (99%) SF-36 questionnaire and 69 (89%) Physical Functioning Interview. Of the 53 subjects who have completed the Year 3 exams, 41 (77%) audiology exams, 43 (81%) neurology exam, 33 (62%) ophthalmology exams, 41 (77%) SF-36 questionnaire and 40 (75%) Physical Functioning Interview. Of the 25 subjects who have completed the Year 4 exams, 25 (100%) audiology exams, 24 (96%) neurology exams, 15 (60%) ophthalmology exams, 23 (92%) SF-36 questionnaire and 24 Physical Functioning Interview.

A review of the Cranial and Spinal CRFs can be found under Task 2 E. Forty-one (89%) of the 46 subjects enrolled from the previous study have provided blood and tumor samples and analysis has been completed. Blood and tumor samples from 41 (91%) new subjects have been collected.

d. All enrolled subjects will be seen for yearly examinations: Completed

Data collection was completed; there are no more yearly examinations.

Task 5. Interim Analysis (months 12-18

a. Interim statistical analysis and data obtained from initial audiometric, MRI studies, and clinical evaluations will be performed: Completed

Preliminary data analysis has begun. Currently, we are in the process of cleaning the data. Each subject is reviewed individually to clearly identify the start point and endpoint of any analysis. Each tumor (either spinal, vestibular schwannoma (VS) or meningioma is the unit of analysis with the start point being the date of each Year 1 exam and the endpoint being either the date of the first VS treatment or date of last follow-up if no treatment was performed. The student biostatisticians cleaned the data up to summer 2005 and performed initial analyses.

Task 6. Final Analysis and Report Writing (months 30-36)

a. Final univariate analysis of data was performed.

Final univariate analysis of the data was performed after receipt of CRFs, data entry was completed, and the data cleaned. Data analysis revealed slow growing tumors, with the growth unrelated to genotype or age at onset of NF2. Tumor growth was more related to NF2 severity, assessed by the number of systems affected by the disease.

b. Final report and initial manuscripts:

All data have been entered into the database and all CRFs logged into our tracking system. Manuscripts on data obtained from the study cover vestibular schwannoma growth, lower cranial schwannoma growth, growth of other NF2-related tumors, audiological changes over time, and quality of life in NF2 subjects and ophthalmological characteristics of subjects.

Key Research Accomplishments

- ❖ Developed an international consortium of clinical centers with expertise in NF2.
- ❖ Established standardized study protocol for multi-institutional, multi-national natural history study.
- ❖ Developed NF2 specific database which includes clinical, radiographical, audiometrical, ophthalmologic, quality of life, and molecular biology/genetic information.
- ❖ Developed standard operating procedure for digital analysis of MRIs utilizing information from a variety of MRI machines from different manufacturers.

Reportable Outcomes

CONFERENCES

- ✓ Steering Committee Meeting, June 4, 2002:
  Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators
- ✓ Steering Committee Meeting, June 1, 2003
  Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators
- ✓ Steering Committee Meeting, June 4, 2004:
  Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators
- ✓ Steering Committee Meeting, June 5, 2005:
  Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators

PRESENTATIONS

- ✓ American Academy of Otolaryngology Head & Neck Surgery Meeting, September 22-25, 2002
  Volumetric Analysis of Vestibular Schwannomas in NF2.
- ✓ The Auditory Brainstem Implant and Neurofibromatosis Type 2. AAO-HNS Annual Meeting & OTO EXPO, New York, NY. September 22, 2004 (course)
- ✓ ABR Change Over Time in Neurofibromatosis Type 2. AAO-HNS Annual Meeting & OTO EXPO, New York, NY. September 22, 2004
- ✓ Lower Cranial Nerve Schwannomas in NF2. AAO-HNS Annual Meeting, September 17, 2006, Toronto, Ontario, Canada.

PUBLICATIONS

- ✓ Magnetic resonance Imaging Scanner Reliability for Measuring Changes in Vestibular Schwannoma Size. Otol Neurotol. 2003 Jul; 24(4):666-70; discussion 670-1.

- ✓ Hearing Changes After Diagnosis in Neurofibromatosis Type 2. Otol Neurotol. 2004 Mar; 25(2): 150-4.

- ✓ Vestibular Schwannoma Growth Rates in Neurofibromatosis Type 2 Natural History Consortium Subjects. Otol Neurotol. 2004 Sept; 25(5):811-7.

Conclusions

The infrastructure necessary for this project to be successful was assembled. A consortium of nine international sites with clinical expertise in NF2 was established. All sites received copies of standardized protocols for all data collection and a centralized database to store all information was created. Subject enrollment had been difficult due to the delay in achieving Army approval of the informed consent forms for each institution. Much effort was given to ensuring that the MRI facilities used by study participants were compatible with WorldCare's systems.

References

None

Appendices

None